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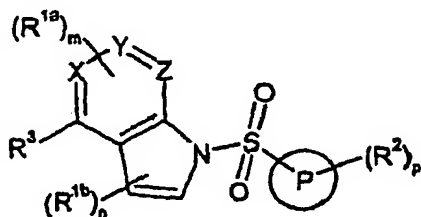
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(54) Title: **SULPHONYL COMPOUNDS WITH 5-HT₆ RECEPTOR AFFINITY**



(I)

(57) Abstract: The present invention relates to novel sulphonyl compounds of the formula (I): having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS and other disorders.

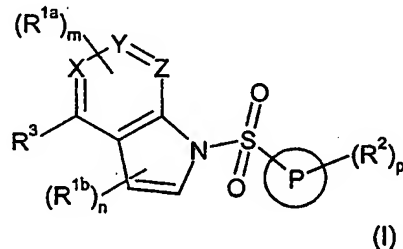
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SULPHONYL COMPOUNDS WITH 5-HT₆ RECEPTOR AFFINITY

This invention relates to novel sulphonyl compounds having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS and other disorders.

WO 98/27081, WO 99/02502, WO 99/37623, WO 99/42465 and WO 01/32646 (SmithKline Beecham plc) disclose a series of aryl sulphonamide and sulfoxide compounds as 5-HT₆ receptor antagonists and which are claimed to be useful in the treatment of various CNS disorders. WO 01/39777 (Osi Pharmaceuticals) describes a series of substituted pyrrolo [2,3-b] pyrimidines as selective adenosine A₁, A_{2a} and A₃ receptor antagonists. WO 99/65908 and WO 99/65909 (Pfizer) describe the use of 7H-pyrrolo [2,3-d] pyrimidine-5-bromo-7-(phenylsulfonyl)-4-(1-piperidinyl) and 7H-pyrrolo [2,3-d] pyrimidine-5-iodo-7-(phenylsulfonyl)-4-(1-piperidinyl) as intermediates in the preparation of protein tyrosine kinases such as Janus Kinase 3. WO 99/28313 (Merck) describe a series of 1,2,3,4-tetrahydroisoquinolines and homologous compounds as farnesyl protein-transferases for chemotherapeutic applications.

A structurally novel class of compounds has now been found which also possess 5-HT₆ receptor affinity. The present invention therefore provides, in a first aspect, use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof:



wherein:

P is aryl or heteroaryl;

25 R^{1a} and R^{1b} independently represent halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkanoyl, CN, CF₃, OCF₃, phenyloxy, benzyloxy or C₃₋₆ cycloalkyloxy;

R² is halogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphinyl, C₁₋₆ alkylsulphonoyl, C₁₋₆ alkanoyl, CN, CF₃, OCH₂CF₃, OCF₃, hydroxy, hydroxyC₁₋₆ alkyl, hydroxyC₁₋₆ alkoxy, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkoxyC₁₋₆ alkoxy, nitro, amino, N(C₁₋₆ alkyl)₂,

30 NHC₁₋₆ alkyl, C₁₋₆ alkylamino or diC₁₋₆ alkylamino, C(O)OR⁴ (where R⁴ is hydrogen or C₁₋₆ alkyl), CONR⁵R⁶ or NR⁵COR⁶, (where R⁵ and R⁶ are independently hydrogen, C₁₋₆ alkyl or R⁵ and R⁶ combine together to form a 5- to 7- membered azacyclic ring optionally containing an additional heteroatom selected from nitrogen, sulphur or oxygen), or aryl or heteroaryl (both of which may be optionally substituted by groups as defined for R^{1a} and R^{1b} above);

35 R³ is a 5- to 7-membered heterocyclic ring or a bicyclic heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen, said ring being optionally C- and/or N-substituted by one or more C₁₋₆ alkyl groups;

m and n independently represent an integer from 0 - 4;

p represents an integer from 0 – 5;

X, Y and Z independently represent nitrogen or carbon, provided that one or two of X, Y and Z represent nitrogen;

in the manufacture of a medicament for the treatment or prophylaxis of depression, anxiety,

- 5 Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment and schizophrenia.

As a second aspect of the present invention we provide a compound of formula (IA) or a pharmaceutically acceptable salt thereof which is a compound of formula (I) wherein R^{1a}, R^{1b}, R²,

- 10 R³, m, n, p, P, X, Y and Z are as defined above, with the proviso that the compound of formula (IA) is not

5-bromo-7-(phenylsulfonyl)-4-(1-piperidinyl)-7H-pyrrolo [2,3-d] pyrimidine; or

5-iodo-7-(phenylsulfonyl)-4-(1-piperidinyl)-7H-pyrrolo [2,3-d] pyrimidine.

- 15 Alkyl groups, whether alone or as part of another group, may be straight chain or branched and the groups alkoxy and alkanoyl shall be interpreted similarly. Alkyl moieties are more preferably C₁₋₄ alkyl, eg. methyl or ethyl. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

- 20 The term "aryl" includes phenyl and naphthyl.

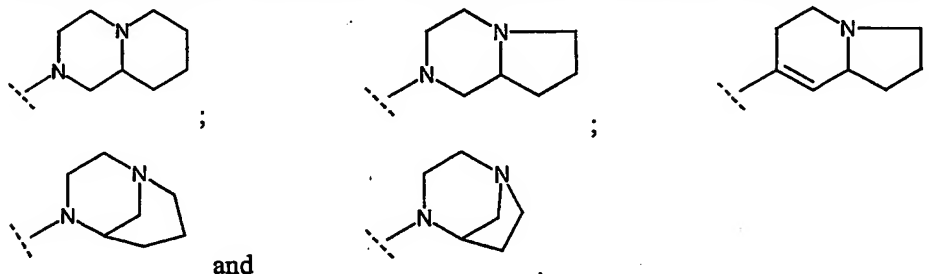
The term "heteroaryl" is intended to mean a 5 or 6 membered monocyclic aromatic or a fused 8-10 membered bicyclic aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such monocyclic aromatic rings include thienyl,

- 25 furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such fused aromatic rings include benzofused aromatic rings such as quinoliny, isoquinoliny, quinazolinyl, quinoxaliny, cinnoliny, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, 30 benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like. Heteroaryl groups, as described above, may be linked to the remainder of the molecule via a carbon atom or, when present, a suitable nitrogen atom except where otherwise indicated above.

- 35 It will be appreciated that wherein the above mentioned aryl or heteroaryl groups have more than one substituent, said substituents may be linked to form a ring, for example a carboxyl and amine group may be linked to form an amide group.

- 40 The term 5- to 7-membered heterocyclic ring is intended to mean a non aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Such rings may be partially unsaturated. Suitable examples of 5- to 7-membered heterocyclic rings include piperidinyl, tetrahydropyridinyl, pyrrolidinyl, morpholinyl, azepanyl, diazepanyl and piperazinyl. A 5- to 7-membered heterocyclic ring, as described above, may be linked to the remainder of the molecule via a carbon atom or a suitable nitrogen atom.

When R^3 is a bicyclic heterocyclic ring, representative examples of such groups are:



Preferably, P represents phenyl, pyridyl or pyrazolyl, more preferably phenyl.

5 Preferably, m represents 0.

Preferably, n represents 0.

Preferably, p represents 0 or 1, more preferably 1.

When present, R^{1a} and R^{1b} preferably independently represent halogen, a C_{1-6} alkyl group, CF_3 , CN or a C_{1-6} alkoxy group.

10 Preferably, R^2 represents halogen, C_{1-6} alkyl, trifluoromethoxy or trifluoromethyl, more preferably halogen.

Preferably, R^3 has up to 2 substituents.

Preferably, R^3 represents piperazinyl, more preferably unsubstituted piperazinyl.

Preferably, X and Y both represent carbon and Z represents nitrogen.

15

Preferred compounds according to the invention include example E1 as shown below, or a pharmaceutically acceptable salt thereof.

20 The compounds of formula (I) can form acid addition salts thereof. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, 66, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

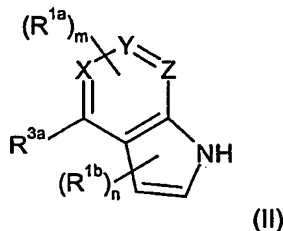
25 The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be solvated, eg. as the hydrate. This invention includes within its scope stoichiometric solvates (eg. hydrates) as well as compounds containing variable amounts of solvent (eg. water).

30 Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. diastereomers and enantiomers) and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by

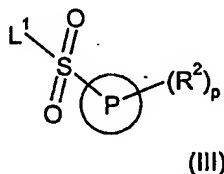
stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

The present invention also provides a process for the preparation of a compound of formula (IA) or a pharmaceutically acceptable salt thereof, which process comprises:

- (a) reacting a compound of formula (II)



- 10 wherein R^1 , m , X , Y and Z are as defined above and R^{3a} represents an R^3 group as defined above optionally protected with a suitable protecting group, eg. t-butoxycarbonyl (Boc), with a compound of formula (III)



- 15 wherein P , R^2 and n are as defined above and L^1 represents a suitable leaving group such as a halogen atom (eg. fluorine or chlorine); and as necessary, deprotecting a compound of formula (IA) which is protected;

- (b) deprotecting a compound of formula (IA) which is protected; or

20

- (c) interconversion to other compounds of formula (IA);

and thereafter optionally forming a pharmaceutically acceptable salt.

- 25 Process (a) typically comprises the use of a suitable base, eg. potassium t-butoxide in a suitable solvent, eg. tetrahydrofuran.

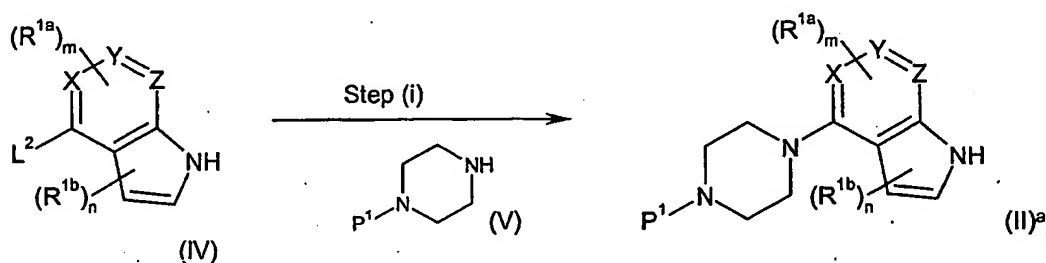
In process (b), examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Suitable amine protecting groups include sulfonyl (e.g. tosyl), acyl (e.g. acetyl, 2',2',2'-trichloroethoxycarbonyl, benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis (e.g. using an acid such as hydrochloric or trifluoroacetic acid) or reductively (e.g. hydrogenolysis of a benzyl group or reductive removal of a 2',2',2'-trichloroethoxycarbonyl group using zinc in acetic acid) as appropriate. Other suitable amine protecting groups include trifluoroacetyl ($-\text{COCF}_3$) which may be removed by base catalysed hydrolysis or a solid phase

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resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker), which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid.

- 5 Process (c) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, nucleophilic or electrophilic aromatic substitution, ester hydrolysis or amide bond formation.

- 10 Compounds of formula (II) wherein R^3 represent piperazinyl may be prepared in accordance with the following process:



- 15 wherein R^{1a} , R^{1b} , m , n , X , Y and Z are as defined above, L^2 represents a suitable leaving group such as a halogen atom (eg. chlorine or fluorine), P^1 represents a suitable protecting group, such as t-butoxycarbonyl.

- 20 Step (i) typically comprises the use of a suitable solvent, eg. dimethylformamide in the presence of a suitable base, eg. using an excess of a compound of formula (V).

- It will be appreciated that compounds of formula (II) wherein R^3 represents N-linked groups other than piperazinyl may be prepared in an analogous manner to that described in the above process.

- 25 Compounds of formulae (II), (III), (IV) and (V) are commercially available, may be prepared using procedures described herein or by analogous methods thereto or according to known methods.

- 30 Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

- 35 Compounds of formula (I) and their pharmaceutically acceptable salts have affinity for the 5-HT₆ receptor and have potential use in the treatment of certain CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, cognitive memory disorders (e.g. Alzheimers disease, age related cognitive decline and mild cognitive impairment), Parkinsons Disease, ADHD (Attention Deficit Disorder/Hyperactivity Syndrome), sleep disorders (including disturbances of Circadian rhythm), feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines,

schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of certain GI (gastrointestinal) disorders such as IBS (Irritable Bowel Syndrome).

- 5 Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of the above disorders. In particular the invention provides for a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of depression, anxiety and cognitive memory disorders

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The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

- 15 In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment or prophylaxis of the above disorders.

- 20 In order to use the compounds of formula (I) in therapy, they will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice.

- A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

- 25 Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tableting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

- 35 Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

- 40 For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised

- before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.
- 10 The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

- The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 200 mg, for example 20 to 40 mg; and such unit doses will preferably be administered once a day, although administration more than once a day may be required; and such therapy may extend for a number of weeks or months.

- 20 All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

- 25 The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1

4-(1*H*-Pyrrolo[2,3-*b*]pyridin-4-yl)-piperazine-1-carboxylic acid *tert*-butyl ester (D1)

- A mixture of 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (100 mg, 0.66 mmol) [see Clark *et al.* J. Chem. Soc. Perkin Trans. 1 1974, 2270 for preparation] and piperazine-1-carboxylic acid *tert*-butyl ester (600 mg, 3.22 mmol) in DMF was heated to 150 °C for 4 h. After allowing to cool to room temperature, DCM was added and the organic phase then washed with water, brine, dried and concentrated *in vacuo*. Purification by column chromatography gave the title compound (D1) (70 mg) as a clear paste; δ H (CDCl₃)/ppm 1.50 (9H, s), 3.47 (4H, t, J = 4.9 Hz), 3.66 (4H, t, J = 5.0 Hz), 6.43 (1H, d, J = 5.6 Hz), 6.48 (1H, d, J = 3.6 Hz), 7.18 (1H, d, J = 3.6 Hz), 8.11 (1H, d, J = 5.5 Hz), 9.40 (1H, br s); MS: *m/z* (M-H⁺) 301.

Description 2

4-[1-(3-Chlorobenzenesulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]-piperazine-1-carboxylic acid *tert*-butyl ester (D2)

- To an ice-cooled solution of 4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-piperazine-1-carboxylic acid *tert*-butyl ester (D1) (40 mg, 0.13 mmol) in THF (3 mL) was added dropwise *t*-BuOK (0.15 mL, 0.15 mmol, 1.0 M in THF). After stirring for 20 min at this temperature, a solution of 3-

chlorobenzenesulfonyl chloride (33 mg, 0.16 mmol) in THF (2 mL) was added dropwise and the mixture allowed to warm to room temperature. Water was added after 3 h and the mixture extracted with diethyl ether and the organic phase dried. Evaporation of solvent was followed by purification by column chromatography to give the title compound (D2) as an orange gum (30 mg); δ H (CDCl₃)/ppm 1.48 (9H, s), 3.37 (4H, t, J = 5.0 Hz), 3.61 (4H, t, J = 5.1 Hz), 6.51 (1H, d, J = 5.6 Hz), 6.60 (1H, d, J = 4.1 Hz), 7.41 (1H, t, J = 8.0 Hz), 7.52 (1H, m), 7.57 (1H, d, J = 4.0 Hz), 8.09 (1H, m), 8.19 (1H, t, J = 0.5 Hz), 8.21 (1H, t, J = 5.7 Hz); MS: m/z (M+H⁺) 477.

Example 1

10 4-[1-(3-Chlorobenzenesulfonyl)-1H-pyrrolo[2,3-b]pyridin-4-yl]-piperazine hydrochloride (E1)

4-[1-(3-Chlorobenzenesulfonyl)-1H-pyrrolo[2,3-b]pyridin-4-yl]-piperazine-1-carboxylic acid *tert*-butyl ester (D2) (25 mg, 0.05 mmol) was exposed to 20 % TFA in DCM for 1 h. Evaporation *in vacuo*, treatment with 1M HCl in diethyl ether in the presence of methanol and evaporation *in vacuo* gave the title compound (E1) as a clear paste (19 mg); δ H (CD₃OD)/ppm 3.48 (4H, t, J = 4.3 Hz), 4.16 (4H, t, J = 4.7 Hz), 7.13 (1H, d, J = 7.2 Hz), 7.24 (1H, d, J = 4.2 Hz), 7.67 (1H, t, J = 8.0 Hz), 7.83 (1H, m), 7.91 (1H, d, J = 4.0 Hz), 8.11 (1H, m), 8.16 (1H, d, J = 7.1 Hz), 8.26 (1H, m); MS: m/z (M+H⁺) 377.

20 Pharmacological data

Compounds can be tested following the procedures outlined in WO98/27081.

The compound of Example E1 was tested and showed good affinity for the 5-HT₆ receptor, having pK_i values > 8 at human cloned 5-HT₆ receptors.

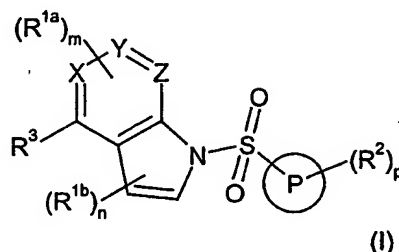
25 Abbreviations

TFA	trifluoroacetic acid
DCM	dichloromethane
DMF	dimethylformamide
THF	tetrahydrofuran

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Claims:

1. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof:



wherein:

P is aryl or heteroaryl;

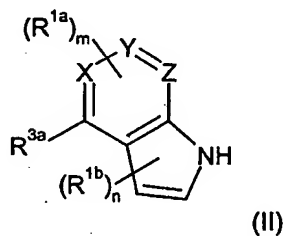
- R^{1a} and R^{1b} independently represent halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkanoyl, CN, CF₃, OCF₃, phenyloxy, benzyloxy or C₃₋₆ cycloalkyloxy;
- R² is halogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulphinyl, C₁₋₆ alkylsulphonyl, C₁₋₆ alkanoyl, CN, CF₃, OCH₂CF₃, OCF₃, hydroxy, hydroxyC₁₋₆ alkyl, hydroxyC₁₋₆ alkoxy, C₁₋₆ alkoxycarbonyl, C₁₋₆ alkoxyC₁₋₆ alkoxy, nitro, amino, N(C₁₋₆ alkyl)₂, NHC₁₋₆ alkyl, C₁₋₆ alkylamino or diC₁₋₆ alkylamino, C(O)OR⁴ (where R⁴ is hydrogen or C₁₋₆ alkyl), CONR⁵R⁶ or NR⁵COR⁶, (where R⁵ and R⁶ are independently hydrogen, C₁₋₆ alkyl or R⁵ and R⁶ combine together to form a 5- to 7- membered azacyclic ring optionally containing an additional heteroatom selected from nitrogen, sulphur or oxygen), or aryl or heteroaryl (both of which may be optionally substituted by groups as defined for R^{1a} and R^{1b} above);
- R³ is a 5- to 7-membered heterocyclic ring or a bicyclic heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, sulphur or oxygen, said ring being optionally C- and/or N-substituted by one or more C₁₋₆ alkyl groups;
- m and n independently represent an integer from 0 - 4;
- p represents an integer from 0 - 5;
- X, Y and Z independently represent nitrogen or carbon, provided that one or two of X, Y and Z represent nitrogen;
- in the manufacture of a medicament for the treatment or prophylaxis of depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive impairment and schizophrenia.

2. A compound of formula (IA) or a pharmaceutically acceptable salt thereof which is a compound of formula (I) wherein R^{1a}, R^{1b}, R², R³, m, n, p, P, X, Y and Z are as defined in claim 1, with the proviso that the compound of formula (IA) is not 5-bromo-7-(phenylsulfonyl)-4-(1-piperidinyl)-7H-pyrrolo [2,3-d] pyrimidine; or 5-iodo-7-(phenylsulfonyl)-4-(1-piperidinyl)-7H-pyrrolo [2,3-d] pyrimidine.

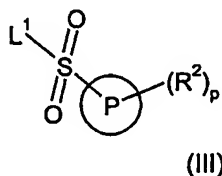
3. A compound as defined in claim 2 wherein P represents phenyl.
4. A compound as defined in claim 2 or claim 3 wherein m and n both represent 0.

5. A compound as defined in any one of claims 2 to 4 wherein p represents 1.
6. A compound as defined in any one of claims 2 to 5 wherein R² represents halogen.
7. A compound as defined in any one of claims 2 to 6 wherein R³ represents unsubstituted piperazine.
8. A compound as defined in any one of claims 2 to 7 wherein X and Y both represent carbon and Z represents nitrogen.
9. A compound as defined in any one of claims 2 to 8 which is 4-[1-(3-chlorobenzenesulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl]-piperazine hydrochloride or a pharmaceutically acceptable salt thereof.
10. A process for the preparation of a compound of formula (IA) or a pharmaceutically acceptable salt thereof, which process comprises:

- (a) reacting a compound of formula (II)



wherein R¹, m, X, Y and Z are as defined in claim 1 and R^{3a} represents an R³ group as defined in claim 1 optionally protected with a suitable protecting group, with a compound of formula (III)



wherein P, R² and n are as defined in claim 1 and L¹ represents a suitable leaving group such as a halogen atom; and as necessary, deprotecting a compound of formula (IA) which is protected;

- (b) deprotecting a compound of formula (IA) which is protected; or
- (c) interconversion to other compounds of formula (IA);

and thereafter optionally forming a pharmaceutically acceptable salt.

11. A compound as defined in any one of claims 2 to 9 for use in therapy.
12. A compound as defined in any one of claims 2 to 9 for use in the treatment of depression,
anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild cognitive
5 impairment and schizophrenia.
13. The use of a compound as defined in any one of claims 2 to 9 or a pharmaceutically
acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of
depression, anxiety, Alzheimers disease, age related cognitive decline, ADHD, obesity, mild
10 cognitive impairment and schizophrenia.
14. A pharmaceutical composition comprising a compound as defined in any one of claims 2
to 9 for use in the treatment of depression; anxiety, Alzheimers disease, age related cognitive
decline, ADHD, obesity, mild cognitive impairment and schizophrenia.
15. A method of treating depression, anxiety, Alzheimers disease, age related cognitive
decline, ADHD, obesity, mild cognitive impairment and schizophrenia which comprises
administering a safe and therapeutically effective amount to a patient in need thereof of a
compound as defined in any one of claims 2 to 9 or a pharmaceutically acceptable salt thereof.
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/01117

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D471/04 A61K31/40 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 65908 A (BROWN MATTHEW FRANK ;PFIZER PROD INC (US); BLUMENKOPF TODD ANDREW) 23 December 1999 (1999-12-23) cited in the application page 40; example V page 42; example M	1-15
A	WO 99 65909 A (BROWN MATTHEW FRANK ;PFIZER PROD INC (US); BLUMENKOPF TODD ANDREW) 23 December 1999 (1999-12-23) cited in the application page 31; example AA page 34; example R	1-15

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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Date of the actual completion of the international search

14 May 2003

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/01117

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02 08178 A (JOSSAN SUKHWINDER ;SAKARIASSEN KJELL S (SE); BIOVITRUM AB (SE); SV) 31 January 2002 (2002-01-31) page 9, line 30 -page 10, line 9; example 4	1-15
Y	WO 01 12629 A (NPS ALLELIX CORP) 22 February 2001 (2001-02-22) the whole document	1-15
Y	EP 0 941 994 A (HOFFMANN LA ROCHE) 15 September 1999 (1999-09-15) abstract; claims 1,4-7,10,11,14,15	1-15
P,X	WO 03 000695 A (ALDOUS DAVIS JOHN ;DEPRETS STEPHANIE DANIELE (GB); PEDGRIFT BRIAN) 3 January 2003 (2003-01-03) page 47; example 1 page 47; example 2	2-5, 10-12,14
P,X	WO 03 000688 A (CLERC FRANCOIS FREDERIC ;DEPRETS STEPHANIE DANIELE (GB); GARDNER C) 3 January 2003 (2003-01-03) page 250; examples 9G,9I page 283; examples 62F,62H	2-5,8, 10-12,14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/01117

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9965908	A	23-12-1999	AP 1021 A	09-11-2001
			AU 3951899 A	05-01-2000
			BG 105129 A	30-11-2001
			BR 9911365 A	13-03-2001
			CA 2335492 A1	23-12-1999
			CN 1305480 T	25-07-2001
			CZ 20004727 A3	13-03-2002
			EP 1087970 A1	04-04-2001
			HR 20000885 A1	31-10-2001
			HU 0102574 A2	28-11-2001
			WO 9965908 A1	23-12-1999
			JP 2002518393 T	25-06-2002
			NO 20006453 A	05-02-2001
			PL 345123 A1	03-12-2001
			SK 18982000 A3	06-08-2002
			TR 200003719 T2	21-03-2001
			US 2002019526 A1	14-02-2002
			ZA 9904004 A	18-12-2000
WO 9965909	A	23-12-1999	AU 4054599 A	05-01-2000
			BG 105122 A	31-10-2001
			BR 9912171 A	10-04-2001
			CA 2335186 A1	23-12-1999
			CN 1305479 T	25-07-2001
			CZ 20004726 A3	13-03-2002
			EP 1087971 A1	04-04-2001
			HR 20000886 A1	31-10-2001
			HU 0103472 A2	28-02-2002
			WO 9965909 A1	23-12-1999
			JP 2002518394 T	25-06-2002
			NO 20006454 A	15-02-2001
			PL 345118 A1	03-12-2001
			SK 18992000 A3	06-08-2002
			TR 200003720 T2	21-03-2001
			ZA 9904003 A	18-12-2000
WO 0208178	A	31-01-2002	AU 8273401 A	05-02-2002
			EP 1301476 A1	16-04-2003
			NO 20030304 A	12-03-2003
			WO 0208178 A1	31-01-2002
			US 2002068732 A1	06-06-2002
WO 0112629	A	22-02-2001	AU 6310300 A	13-03-2001
			CA 2382247 A1	22-02-2001
			EP 1204662 A1	15-05-2002
			WO 0112629 A1	22-02-2001
			JP 2003507380 T	25-02-2003
EP 0941994	A	15-09-1999	EP 0941994 A1	15-09-1999
			AU 752408 B2	19-09-2002
			AU 2038399 A	23-09-1999
			BR 9901095 A	02-05-2000
			CN 1236780 A	01-12-1999
			CZ 9900825 A3	15-09-1999
			HR 990077 A1	29-02-2000
			HU 9900589 A1	28-03-2000
			JP 3231288 B2	19-11-2001
			JP 2000186090 A	04-07-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/01117

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0941994	A	NO 991150 A	13-09-1999
		NZ 334526 A	28-07-2000
		PL 331875 A1	13-09-1999
		SG 78336 A1	20-02-2001
		TR 9900531 A2	21-10-1999
		US 6194410 B1	27-02-2001
		ZA 9901946 A	13-09-1999
WO 03000695	A 03-01-2003	WO 03000695 A1	03-01-2003
WO 03000688	A 03-01-2003	WO 03000688 A1	03-01-2003